Remarks/Arguments

Reconsideration of this application, as amended, is respectfully requested.

I. Status of the Claims

Claims 1 to 27 are pending. Claims 9, 15 to 17, 20, 21 and 24 to 27 have been withdrawn from consideration. Claims 1 to 5, 10 to 14 and 23 were rejected under 35 U.S.C. § 103 as obvious over WO 2000/25786 ("Bao") as evidenced by Rogers et al., Brain Res, 493: 41-50, 1989 ("Rogers") in view of Williams et al., Brain Res, vol. 493. pp. 41-50, 1989 ("Williams") and Patani et al., Chem Rev, vol. 96, pp. 3147-3176, 1996 ("Patani"). Claims 1 to 8, 10 to 14, 18, 19 and 23 were provisionally rejected for non-statutory double patenting over Claims 1, 4 and 18 of copending U.S. Application No. 10/579,261 ("the '261 application") in view of Williams and Patani et al., Chem Rev, vol. 96, pp. 3147-3176, 1996. No claim was allowed.

This Amendment cancels claim 15 to17 and 21, rendering the rejection of these claims moot. This Amendment also amends claims 1, 12, 18 and 22 to direct these claims to only Group I subject matter. Claims 1 and 12 to 14 have also been amended to remove unsubstituted alkoxy from the definition of R^{2a}, R^{2b} and R^{2c}. Upon entry of this Amendment, claims in the application will be claims 1, 14, 18 to 20 and 22 to 27.

II. Obviousness Rejection

Claims 1 to 5, 10 to 14 and 23 have been rejected as obvious over Bao in view of Rogers, Williams and Patani. Applicants submit the claims as amended are non-obvious over Bao, Rogers, Williams and Patani.

The Examiner has not established a prima facie case of obviousness. First, the Examiner bases his obviousness argument beginning with Example 18. However, there is no indication from Bao that Example 18, as opposed to the other examples, would clearly be the starting reference point from which a skilled artisan might identify a problem and pursue potential solutions. Second, and contrary to the Examiner's assertion, the focus of Bao from the viewpoint of the ordinarily skilled artisan is on autoimmune diseases and cardiac arrhymia. *See* the abstract therein. Senile dementia is mentioned among a list of other indications.

One skilled in art would in no way be motivated to select Example 18 among the other compounds described in Bao and modify it by interchanging the phenyl group on the central piperidine ring with pyridyl. The Examiner alleges that Williams and Patani provides the necessary motivation,

but Applicants disagree. Williams simply states that when "a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmokinetic properties suitable for making it a viable clinical candidate … The medicinal chemist therefore must modify the compound to reduce or eliminate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as isoteric or bioisosteric replacement". Williams then goes on to identify "classical bioisosteres" in Table 2.9. However, Williams does not indicate that pyridyl can or should be substituted for phenyl at the 4-position of a central piperidine ring and that such substitution would result in compounds having activity as GlyT or potassium channel inhibitors. In fact Williams has nothing to do with these targets and is a general medicinal chemistry text. One skilled in the art with knowledge of Bao would in no way be looking to Williams for specific teachings to modify compounds active against these targets.

Neither does Patani provide the necessary motivation. Patani teaches that substitution of phenyl by pyridyl resulted in compounds with retained activity for the antihistamines mepyramine and isothipendyl and the neuroleptic prothipendyl. Patani makes no teaching or suggestion with respect to the substitution of phenyl by pyridyl on the pipridine core for the targets GlyT or potassium channel inhibitors. Thus, Patani does not provide the necessary motivation to select and modify Example 18 of Bao to arrive at the compounds of the present claims.

Moreover, Applicants have also amended the claims to remove unsubstituted alkoxy from the definition of R^{2a}, R^{2b} and R^{2c}. Thus, the claims no longer encompass the "hypothetical compound" described at page 5 of the Office action. Further, <u>all</u> the examples described in Bao have a methoxy group substituted on the benzamide portion, thus teaching away from the claims as presently amended.

In further support of patentability, Applicants refer the Examiner to Zhao et al., Bioorganic & Medicinal Chemistry Letters 19 (2009) 1488-1491 ("Zhao"), submitted herewith in an Information Disclosure Statement. At page 1490, the first complete paragraph, Zhao states that neither compounds **7j** nor **7n** described therein (4-pyridylpiperidine derivatives) are time-dependent CYP inhibitors which is an issue for **2** (-4-phenylpiperidine derivative). The underlying data is shown in the Declaration of Scott Wolkenberg submitted herewith. Note that three out of the four 4-phenylpiperidine compounds were TDI+ while three out of three of the 4-pyridylpiperdine compounds

were TDI-. This result clearly demonstrates an unexpected superior preclinical profile for the 4-pyridylpiperidine series over the 4-phenylpiperidine series.

Withdrawal of the obviousness rejection over Bao in view of Rogers and Brinker is respectfully requested.

IV. Double Patenting Rejection

Applicants respectfully traverse the obviousness type double patenting rejection of claims 1 to 8, 10 to 14, 18 to 19 and 23 over claims 1, 4 and 18 of the '261 application. For the reasons states above, substitution of a pyridyl for a phenyl at the 4-position of the central piperidine ring is a non-obvious structural change. Neither Williams nor Patani provide the necessary motivation to make this change. The Examiner is again referred to Zhao and the Declaration of Scott Wolkenberg in support of non-obviousness. Withdrawal of the obviousness-type double patenting rejection is respectfully requested.

V. Rejoinder

Applicants submit the rejection of the compound and pharmaceutical composition claims have been overcome. Rejoinder of the method claims pursuant to M.P.E.P. § 821.04 is respectfully requested.

Applicants also submit that Claims 9 and 20 are directed to Group I subject matter.

VI. Conclusion

An early and favorable examination is earnestly solicited.

Respectfully submitted,

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